REMARKS

Claims 1-4 and 7-8 are pending in the present application. Claims 1-4 and 7-8 have been amended. Support for the amendment of these claims to recite "powdered" pharmaceutical composition is found on page 4 of the specification, lines 21-23, that recites "These active compounds are administered as an inhalation with the aid of ... powder inhalers (MPDI)." Further amendments have been made for clarity. No new matter is believed to have been added.

Rejections under 35 U.S.C. §102

Claims 1-4 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by *Keller et al.* ("*Keller*") (WO 9834595, English equivalent to U.S. Patent No. 6,461,591).

MPEP §2131 provides that a claim is deemed anticipated "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference" (emphasis added; MPEP quoting *Verdegaal Bros. v. Union Oil Co. of Claifornia,* 814 F.2d 628, 631 2USPQ2d 1051, 1053 (Fed. Cir. 1987)). Thus, a proper *prima facie case of anticipation* requires that a single reference is provided by the Examiner that discloses each of the claimed elements as interpreted by one of ordinary skill in the art.

Applicants traverse the rejection of Claims 1-4 under 35 U.S.C. § 102(b), and assert that *Keller* does not disclose the claimed pharmaceutical composition comprising a combination of (i) loteprednol or loteprednol etabonate and (ii) β_2 adrenoreceptor agonists. *Keller* merely provides a list of pharmaceutically active compounds that may be included in their aerosol formulations (see Col. 7 of *Keller*).

Nevertheless, Claims 1-4 have been amended to recite "powdered" pharmaceutical compositions, which distinguishes the claimed formulations from formulations taught by *Keller. Keller* discloses only pressure-liquefied propellant mixtures for the preparation of aerosols formulated for administration by using pressurized inhalants (see Table 1, Col. 12 of *Keller* and Examples 1-14, Cols. 11-14 of *Keller*). Again, Applicants point out that *Keller* does not disclose the claimed powdered formulations comprising: (i) loteprednol or loteprednol etabonate and (ii) at

least one β_2 adrenoreceptor agonists. Because pressure-liquefied aerosol formulations are different from powdered formulations recited in Claims 1-4 as amended, Applicants request the withdrawal of the §102(b) rejection.

Rejections under 35 U.S.C. §103

Claims 7 and 8 stand rejected under 35 U.S.C. §103(a) as purportedly unpatentable over *Keller et al.* ("*Keller*") in view of *Doi et al.* ("*Doi*") (WO 98/31343), *Bjermer et al.* ("*Bjermer*"), and *Molen et al. ("Molen").*

MPEP §2143 provides that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the Applicant's disclosure." (MPEP sec. 2143 quoting *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Applicants traverse the rejection of Claims 7 and 8 under 35 U.S.C. § 103(a), and assert that these cited references alone, or in combination, do not suggest the combination of the elements of the present invention recited in Claim 7, directed to a method for treating asthma bronchiale, and Claim 8, directed to a method for the preparation of pharmaceutical compositions for the treatment of asthma bronchiale.
In the following discussion, Applicants will point out deficiencies of each reference, alone or in combination, for teaching the claimed critical combination of (1) loteprednol (or loteprednol etabonate) and (2) β_2 adrenoceptor agonists. In the following discussion, Applicants will point out experimental data contained in the Specification (Tables 1-4) showing unexpected advantages of the present invention, which are believed to have been overlooked by the Examiner.

As explained above, Keller does not disclose the specific pharmaceutical combination recited in Claims 1-4 nor does it suggest the co-administration of the

combination of (i) loteprednol or (loteprednol etabonate) and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents for treating asthma bronchiale (Claim 7) and for preparing such pharmaceutical formulations (Claim 8). In fact, the Office Action states that "Keller does not expressly disclose the employment of the inhalable medicinal aerosol composition comprising the combination as instantly claimed ..." (see lines 1-4, at page 4 of the Office Action).

Bjermer does not disclose the specific pharmaceutical combination recited in Claims 1-4 nor does it suggest the co-administration of the combination of (i) loteprednol (or loteprednol etabonate) and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents for treating asthma bronchiale (Claim 7) and for preparing such pharmaceutical formulations (Claim 8). Infact, *Bjermer* discloses a mixture of (1) classical corticosteroids (e.g., beclomethasone dipropionate (BDP), budesonide (BUD)) and (2) β_2 adrenoceptor agonists (e.g., bambuterol, salmeterol, and formoterol) for treating asthma (see lines 1-2 at page 588 of *Bjermer*; lines 12-15 of *Bjermer*). Applicants point out that disclosing the combination of a classical corticosteroids with a β_2 adrenoreceptor agonist is not the equivalent of disclosing the combination of a loteprednol (or loteprednol etabonate) and a β_2 adrenoceptor agonist because the classical corticosteroids disclosed in *Bjermer* are functionally different from the soft corticosteroids by having a different mechanism of action compared to that of the soft corticosteroids claimed by the Applicants. Thus, if one element of a claimed mixture is different from an element of a mixture taught by the cited reference, then the claimed mixture as a whole must be different from the mixture taught by the cited reference.

Furthermore, Applicants have distinguished the properties of soft corticosteroids (from that of classical corticosteroids) in the Specification by explaining that soft corticosteroids, such as loteprednols or loteprednol etabonates, are more readily metabolized (inactivated) *in vivo* by engaging a different metabolic pathway compared to classical corticosteroids, such as beclomethasone dipropionate (BDP) or budesonide (BUD), which are known to have relatively higher *in vivo* stability resulting in many deleterious side effects experienced by patients (see lines 21-31, at page 2 of the Specification). Applicants have further explained differences in the side effects produced by classical corticosteroids and soft

corticosteroids to distinguish the claimed compositions and methods from the prior art (see lines 10-30, page 7 of the Specification). The claimed combination is especially beneficial for children who are especially sensitive to the deleterious side effects caused by classical corticosteroids, which includes growth retardation, osteoporosis, and an increase in intraocular pressure.

Lastly, neither Doi and *Molen, individually or in combination with any of the cited references, disclose the specific pharmaceutical combination recited in Claims 1-4 nor do they suggest the co-administration of the combination of (i) loteprednol (or loteprednol etabonate) and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents for treating asthma bronchiale (Claim 7) and for preparing such pharmaceutical formulations (Claim 8).* If one were to hypothetically combine the cited references, the result is a mixture of a classical corticosteroid with a β_2 adrenoceptor agonist, which is different from the claimed combination of (1) loteprednol (or loteprednol etabonate) and (2) β_2 adrenoceptor. Thus, absent a teaching from the cited references to combine (1) loteprednol (or loteprednol etabonate) and (2) β_2 adrenoceptor, a *prima facie case* for obviousness has not been established.

Furthermore, Applicants submit that the Office has not fully appreciated the experiments performed by the Applicants, as shown in the Specification. These experiments provide unexpected advantages, resulting from the co-administration of (1) loteprednol (or loteprednol etabonate) and (2) β_2 adrenoceptor agonists. The specification provides data showing synergistic effect caused by the co-exposure to a mixture of (1) loteprednol or loteprednol etabonate; and (2) β_2 adrenoceptor agonists, under *in vitro* and *in vivo* conditions. The specification provides comparative data showing a less deleterious effect by loteprednol in comparison to classical corticosteroids. The specification also provides comparative data showing enhanced therapeutic effect by loteprednol in comparison to classical corticosteroids.

Table 1 of the specification shows *in vitro* synergistic (over-additive) effect (44%) of the mixture of loteprednol and salbutamol on blood cells as measured by the level of inhibition on TNF-alpha release, compared to samples exposed only to either loteprednol (1%) or salbutamol (17%) alone (see page 5 of the Specification).

Table 2 shows *in vivo* synergistic effect (36 - 65%) of a mixture of loteprednol and formoterol on guinea pigs as measured by the level of inhibition of eosinophilia, compared to samples exposed only to either loteprednol (11-22%) or formoterol (4-20%) alone (see page 6 of the Specification).

Table 3 shows gross reduction in thymus mass in rats exposed to classical corticosteroids, including fluticasone (65%), beclomethasone (51%), and budesonide (89%), in comparison to loteprednol (15-28%). This suggests that the co-administration of loteprednol in combination with β_2 adrenoceptor agonists would likely produce the over-additive effect exemplified in Tables 1 and 2 in patients, while providing advantages for avoiding some of the deleterious side effects associated with classical corticosteroids that have been well-documented in the prior art, including the cited references (see page 8 of the Specification).

Table 4 shows enhanced therapeutic breadth after long-term exposure to loteprednol (45.5) in comparison to modest or low therapeutic efficacy observed for classical steroids, such as fluticasone (33) and budesonide (5) (see page 10 of the Specification).

In light of the above discussion, Applicants respectfully request the withdrawal of the rejection of Claims 7 and 8 under 35 U.S.C. §103(a).

CONCLUSION

From the foregoing, further and favorable action in the form of Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions relating to this Amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 838-6671 so that the prosecution of the application may be expedited.

Respectfully submitted,

BUCHANAN INGERSOLL PC

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